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Medicinal Plants with Multiple Effects on Diabetes Mellitus and Its Complications: a Systematic Review

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Abstract

Purpose of Review This systematic review describes evidence concerning medicinal plants that, in addition to exerting hypoglycemic effects, decrease accompanying complications such as nephropathy, neuropathy, retinopathy, hypertension, and/or hyperlipidemia among individuals with diabetes mellitus (DM).

Recent Findings Studies on the antidiabetic mechanisms of medicinal plants have shown that most of them produce hypoglycemic activity by stimulating insulin secretion, augmenting peroxisome proliferator-activated receptors (PPARs), inhibiting α-amylase or α-glucosidase, glucagon-like peptide-1 (GLP-1) secretion, advanced glycation end product (AGE) formation, free radical scavenging plus antioxidant activity (against reactive oxygen or nitrogen species (ROS/RNS)), up-regulating or elevating translocation of glucose transporter type 4 (GLUT-4), and preventing development of insulin resistance.

Summary Not only are medicinal plants effective in DM, but many of them also possess a variety of effects on other disease states, including the complications of DM. Such plants may be appropriate alternatives or adjuncts to available antidiabetic medications.

Keywords Diabetes mellitus · Medicinal plants · Nephropathy · Neuropathy

Introduction

Diabetes mellitus (DM) is one of the most common endocrine diseases worldwide, and the number of people with DM was recorded as 422 million in 2014 [1]. Type 1 DM is caused by impaired insulin secretion, while type 2 DM is related to progressive insulin resistance in the liver and peripheral tissues, as well as relative insulin deficiency [2].

DM along with impaired glucose tolerance is a life-threatening illness that increases the risk of cardiovascular disease by as much as eight times [3]. The disease accounts for 60% of non-invasive amputations in the USA [3], and in 2015, 30.3 million Americans were regarded to have DM, 7.2 million of which were thought to be undiagnosed [4]. In the same year, an estimated 1.6 million deaths were directly attributed to DM and a further 2.2 million deaths were ascribed to high blood glucose [5]. It was also estimated that, by the year 2040, the number of adults with DM would increase to 642 million globally [6]. Higher-than-optimal blood glucose caused deaths, by increasing the risks of cardiovascular and other diseases. Forty-three percent of these deaths occurred before the age of 70 years [1].

Hyperglycemia causes an increase in oxidative stress, resulting in inflammation, activation of the polyol pathway, and damage to various organs of the body [7, 8]. DM requires diagnosis accompanied by medical management with lifestyle modification although currently, no successful causal treatment has been discovered. There are many synthetic drugs for the symptomatic treatment of DM, but none of them are able to

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definitively alleviate the disease origin [9]. Common symptomatic treatments include regular injection of insulin or oral administration of antidiabetic drugs, such as sulfonylureas, α-glucosidase inhibitors, biguanides, thiazolidinediones, dipeptidyl peptidase-4 (DPP4) inhibitors, sodium-glucose co-transporter-2 (SGLT2) inhibitors, glinides, and parenteral administration of glucagon-like peptide-1 (GLP-1) agonists, which can cause moderate to severe side effects [10]. As a result, alternative treatments are urgently needed for more effective management of the disease.

Complementary and alternative medicine (CAM) is increasingly being used as a DM management strategy. In this context, traditional herbal medicine is used across the world for disease treatment [11]. The World Health Organization has recommended that clinicians use herbal drugs to treat DM in addition to its complications. There is no ultimate method available to prevent and treat DM, but strategies are needed to reduce the complications brought about by the disease [12, 13]. Some medicinal plants with antioxidant properties are useful for reducing oxidative stress and its adverse effects [14, 15], and nowadays, some of the available drugs are plant based [16]. Research has shown that a number of antidiabetic plants, apart from their hypoglycemic activity, have other useful properties such as antihypertensive, nephroprotective and retinoprotective activities which may be useful against the most common complications of DM. Thus, consumption of these plants may well be exploited in the control of DM and its complications [17, 18]. Hence, the purpose of this article is to systematically review the medicinal plants that are useful in the management of DM and its accompanying complications.

Materials and Methods

To conduct this review, firstly the complications caused by DM were addressed. Subsequently, underlying antidiabetic mechanisms of medicinal plants were reviewed under general thematic headings. For this purpose, the articles indexed in *PubMed*, *Scopus*, *Web of Science*, *MEDLINE*, *Google Scholar*, *Web of Science* (*SCOPUS*), *EBSCO Academic Search*, *Cochrane Central Register of Controlled Trials* (*CENTRAL*), and the *Chinese Network Knowledge Infrastructure* (*CNKI*), published prior to 2018, and retrieved using the keywords "hypertension," "retinopathy," "neuropathy," and "nephropathy" or "medical plants for diabetic hypertension or retinopathy or nephropathy or neuropathy" were reviewed. Articles containing plants affecting one or more of the above items were selected.

A total of 36,000 publications were retrieved by the first selection process. Out of these publications, 305 articles identified in medical plants were examined against DM and/or diabetic complications (hypertension, retinopathy, nephropathy, neuropathy, and/or hyperlipidemia). After a more detailed review of these articles, 89 relevant papers were selected and their applicable findings summarized in tabular form.

Results

Medicinal Herbs Effective on Diabetes

The use of antioxidants and the reduction and control of blood glucose significantly reduce the complications associated with DM [12, 13]. Consequently, medicinal plants with antioxidant properties are employed to restrict oxidative stress and its adverse effects [14, 19]. A number of medicinal plants with antidiabetic and antihyperlipidemic effects are known to be effective in preventing and treating DM.

Antidiabetic Plant Mechanisms

There are several fundamental modes of action for natural products in DM [20]. The principal mechanisms include those that act by stimulating insulin secretion, augmenting peroxisome proliferator-activated receptors (PPARs), inhibiting α-amylase or α-glucosidase, inhibiting the secretion of the incretin, GLP-1, inhibiting advanced glycation end-product (AGE) formation, free radical scavenging plus antioxidant activity (against reactive oxygen or nitrogen species (ROS/RNS)), up-regulating or elevating translocation of glucose transporter type 4 (GLUT-4), and preventing development of insulin resistance (Fig. 1).

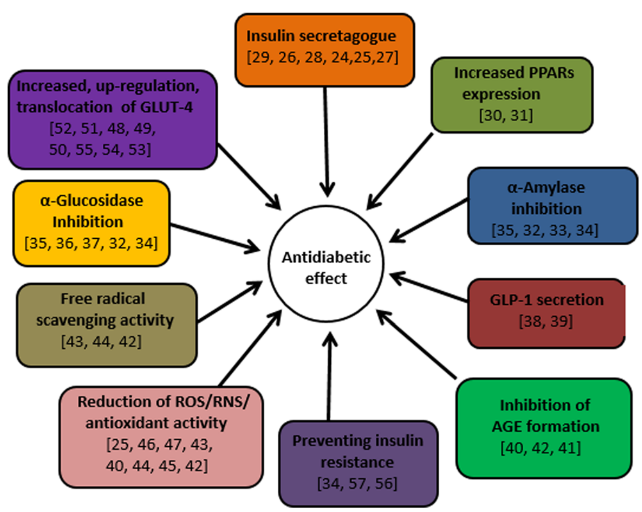

Fig. 1 Diagram depicting some of the principle plant-derived mechanisms of antidiabetic activity. GLUT-4, insulin-regulated glucose transporter type 4; ROS, reactive oxygen species; RNS, reactive nitrogen species; AGE, advanced glycation end products; DPP4, dipeptidyl peptidase; GLP-1, glucagon-like peptide-1 (incretin); PPARs, peroxisome proliferator-activated receptors

Insulin Secretagogues

Some plants or their constituents stimulate insulin secretion. They include *Panax ginseng* [21] and the diosgenin component in Fenugreek (*Trigonella foenum graecum*) [22–24] which also increases glucose metabolism not only by stimulating adipocyte differentiation but also via a reduction of inflammation in adipocytes [25]. There is in addition, an insulin secretagogic action of the compound *S*-methyl cysteine sulfoxide which has been isolated from the onion plant (*Allium cepa*) [26].

Increased Expression of Peroxisome Proliferator-Activated Receptors

In bitter melon (*Momordica charantia* L.), 9*cis*,11*trans*,13-*trans*-conjugated linolenic has been found to activate PPAR-α in rat tissues [27]. In addition, momordin extracted from bitter melon, increases the expression of human PPAR-δ mRNA and the production and activation of PPAR-δ is further upregulated through PPAR-δ promoter activity [28].

α-Amylase and α-Glucosidase Inhibition

Azadirachtolide, isolated from *Azadirachta indica* (also known as Neem tree) has been shown to exhibit anti-hyperglycemic and anti-lipidemic actions in diabetic rats. Furthermore, an inhibitory activity of azadirachtolide on α-amylase and α-glucosidase has been demonstrated, suggesting that this *A. indica* constituent is potentially beneficial in the management of DM associated with an abnormal lipid profile coupled with related cardiovascular complications [29]. Moreover, the limonoids azadiradione and gedunin plus the tetranortriterpenoid compound meliacinolin isolated from *A. indica*, are also inhibitory on both α-amylase and α-glucosidase further indicating that this medicinal plant has a propensity to reduce post-prandial hyperglycemia in the diabetic condition [30, 31]. Additionally, extracts from cinnamon bark species possess inhibitory activity against intestinal α-glucosidase and pancreatic α-amylase [32] and even after chronic extract administration, α-glucosidase activity remains at a low level, so this natural product has promise in DM [33]. What is more, an extract of onion (*A. cepa*) containing the phenolic compound quercetin, also possesses α-glucosidase inhibitory activity [34].

Increased Glucagon-Like Peptide-1 Secretion

It has been demonstrated in vitro and in vivo that the saponin ginsenosides present in *P. ginseng* stimulate GLP-1 secretion, and this incretin reduces hyperglycemia significantly contributing toward an antidiabetic effect [35]. Apart from *P. ginseng*, other medicinal plants including *Anemarrhena asphodeloides*, *Citrus aurantium*, *Bupleurum falcatum*, and *Gentiana scabra* also have GLP-1 secretogogic activity [36].

Inhibition of Advanced Glycation End-Product Formation

AGEs cause inflammation and have a crucial role in generating diabetic complications. In light of this, catalpol isolated from *Rehmannia glutinosa* restrains AGE-mediated inflammation by inhibiting ROS production and NADPH-oxidase activity, and this is considered to prevent AGE-mediated problems in DM [37]. An extract from *A. indica* also inhibits AGE formation in addition to oxidative stress, and it is thought to have a protective effect in diabetic kidney disease [38]. Similarly, a *Piper auritum* leaf extract has been reported to have concomitant antioxidant as well as AGE inhibitory activities [39].

Free Radical Scavenging Activity

An extract from *R. glutinosa* rhizome displayed free radical scavenging activity reducing the level of ROS intracellularly in addition to diminishing pro-inflammatory gene expression, and this finding has been advocated as a therapeutic possibility for DM [40]. Likewise, *T. foenum graecum* (Fenugreek) seeds boost antioxidant status in the blood suggesting that perturbed free radical metabolism in the diabetic condition may be returned to normal [41]. It is of note in this regard that a range of other plants used to treat DM, exhibit activity in the 2,2-diphenyl-1-picrylhydrazyl (DPPH) test for free radical scavengers [39].

Reduction of Antioxidant/ROS/RNS Activity

Invariably, studies on free radical scavengers are performed in the context of antioxidant activity. Thus, *R. glutinosa* has strong free radical scavenging effects which are coincident with a reduced production of ROS [40], and this is attributable to catalpol [37]. Fenugreek increases lipid peroxidation and blood antioxidants in diabetic rats [41], and its constituent trigonelline acts by affecting ROS [22] while the steroidal saponin, diosgenin, also present in yam (Dioscoreaceae family), modulates oxidative stress [42]. The ginsenoside-Rg1 component of *P. ginseng* improves angiogenesis in diabetic ischemic rat hindlimb which is believed to be through increased activation of endothelial nitric oxide synthase (eNOS) [43]. Another *P. ginseng* constituent, 20(S)-ginsenoside Rg(3), produces positive effects on diabetic renal damage which have been assigned to inhibition of NMDA receptor-mediated nitrosative stress [44]. It is also noteworthy that there are other examples of antidiabetic plant-induced antioxidant activity [39].

Table 1 Medicinal plants with multiple functions in diabetes mellitus

Scientific name	Family	Hyperglycemia	Nephropathy	Neuropathy	Retinopathy	Hypertension	Hyperlipidemia	Reference
Anacardium occidentale (leaf)	Anacardiaceae	☑	☑					[58]
Achillea milefolium (leaf)	Asteraceae	☑				☑	☑	[59, 60]
Althea officinalis (root)	Malvaceae	☑				☑		[61]
Allium iranicom (leaf, bulb)	Liliaceae	☑					☑	[62••]
Allium cepa (leaf, bulb)	Liliaceae	☑				☑	☑	[63, 64]
Allium sativum (leaf, bulb)	Liliaceae	☑	☑			☑	☑	[65, 66]
Aloe vera (leaf)	Liliaceae	☑				☑	☑	[67–72]
Anethum graveolens (leaf, seed)	Apiaceae	☑				☑	☑	[73, 74]
Angelica sinensis	Umbelliferae			☑				[75]
Annona squamosa (leaf)	Annonaceae	☑				☑	☑	[57, 76]
Annona muricata (leaf)	Annonaceae		☑	☑	☑	☑		[58]
Astragalus membranaceus	Fabaceae		☑			☑		[59–82]
Apium graveolens (leaf)	Umbellifera	☑				☑	☑	[83, 84]
Artemisia vulgaris (leaf)	Compositae	☑				☑		[85]
Arctium loppa (root)	Compositae	☑				☑	☑	[62••]
Avena sativa (fruit)	Germinaceae	☑				☑	☑	[86]
Berberris vulgaria (root/fruit)	Berberidaceae	☑				☑	☑	[87, 88]
Boerhaavia diffusa (leaf)	Nyctaginaceae	☑						[89, 90]
Boswellio carteri (resin)	Burceraceae	☑				☑		[91]
Bougainvillea spectabilis (leaf)	Nyctaginaceae	☑						[92]
Bridelia ndellensis (leaf)	Euphorbiaceae	☑						[93]
Camellia sinensis	Green tea		☑		☑			[94–98]
Canavalia ensiformis (seeds)	Leguminosae	☑	☑			☑	☑	[99, 100]
Casearia esculenta	Flacourtiaceae	☑	☑					[101–103]
Cassia kleinii (leaf)	Caesalpiniaceae	☑						[104]
Castanospermum austral (seeds)	Fabaceae	☑				☑		[105]
Capsicum frutescens	Solanaceae			☑				[106–110]
Catharanthus roseus (leaf)	Apocyaceae	☑						[111]
Chicorium intybus (root)	Compositae	☑				☑	☑	[112]
Citrus limon (fruit)	Rutaceae	☑				☑	☑	[113]
Cinnamomum verum (bark)	Lauraceae	☑				☑	☑	[114]
Cinnamonum cassia	Lauraceae	☑						[115]
Cinnamomum zeylanicum	Lauraceae		☑					[116]
Citrus aurantium (fruit)	Rutaceae	☑				☑	☑	[117, 118]
Citrus paradise (fruit)	Rutaceae	☑				☑	☑	[119, 120]
Coccinia indica (fruit)	Cucurbitaceae	☑						[121]
Colocassia esculenta	Araceae		☑					[122]
Cocculus hirsutus (leaf)	Menispermaceae	☑	☑					[123]
Coscinium fenestratum (stem)	Menispermaceae	☑						[124]
Coriandrum sativom (fruit)	Umbelliferae	☑					☑	[62••]
Cornus mas (fruit)	Cornaceae	☑				☑	☑	[125, 126]
Crataegus microphylla (leaf/fruit)	Rosaceae	☑				☑	☑	[127]

Table 1 (continued)

Scientific name	Family	Hyperglycemia	Nephropathy	Neuropathy	Retinopathy	Hypertension	Hyperlipidemia	Reference
Cryptomeria japonica (leaf)	Cupressaceae	☑				☑		[128]
Cucumis melo (fruit)	Cucurbitaceae	☑				☑	☑	[129, 130]
Curcubita pepo (fruit)	Curcubitaceae	☑				☑	☑	[131]
Cynara cardunculus (flower)	Asteraceae	☑					☑	[132]
Curcuma longa	Zingiberaceae	☑			☑			[133, 134]
Daucus carota (fruit)	Umbelliferae	☑				☑		[135]
Descurainia sophia (seeds)	Brassiacaceae	☑				☑		[136]
Desmodium styracifolium (flower)	Fabaceae	☑				☑		[137]
Dioscorea dumetorum (stem)	Dioscoreaceae	☑				☑		[138, 139]
Dioscorea cayenensis	Dioscoreaceae		☑					[122]
Ficus hispida (bark)	Moraceae	☑						[140, 141]
Fish oil			☑			☑		[142–144]
Ganoderma lucidum	Ganodermataceae		☑					[145]
Ginkgo biloba	Ginkgoaceae		☑		☑	☑		[146–149]
Gymnema montanum	Asclepiadaceae		☑					[150]
Glycine max			☑			☑		[151]
Hypoxis hemerocallidea Fisch. Mey.	Hypoxidaceae	☑						[152, 153]
Juglans regia	Juglandaceae							[154]
Linum usitatissimum	Linaceae	☑	☑					[155, 156]
Lycium barbarum	Solanacaea	☑						[157]
Momordica charantia	Cucurbitacaea		☑	☑				[158]
Murraya koenigii Linn.	Rutaceae	☑						[159]
Oenothera biennis	Onagraceae			☑				[160]
Olea europaea	Oleaceae		☑					[161, 162]
Paeonia suffruticosa	Paeoniaceae				☑			[163]
Panax ginseng (root)	Araliaceae	☑	☑					[164]
Panax notoginseng	Araliaceae		☑					[165, 166]
Pinus pinaster	Pinaceae				☑			[167, 168]
Polygonatum odoratum	Asparagaceae		☑					[169]
Propolis			☑					[170, 171]
Pueraria lobata	Fabaceae							[172, 173]
Punica granatum	Lythraceae					☑		[174]
Rehmannia glutinosa	Orobanchaceae							[175, 176]
Rheum officinale	Polygonaceae		☑					[177]
Rhodiola rosea	Crassulaceae							[115]
Salvia hispanica	Lamiaceae					☑		[178]
Salvia miltiorrhiza	Lamiaceae		☑			☑		[179–181]
Silybum marianum	Asteraceae		☑					[182]
Syzyguim cumini (leaf/fruit/seeds/bark/tea)	Myrtaceae	☑	☑	☑				[183–185]
Terminalia chebula (seeds)	Combretaceae	☑	☑					[186]
Terminalia catappa (fruit)	Combretaceae	☑	☑			☑		[187]
Tinospora cordifolia	Menispermaceae			☑				[188]
Trigonella foenum graecum	Fabaceae				☑			[189, 190]

Table 1 (continued)

Scientific name	Family	Hyperglycemia	Nephropathy	Neuropathy	Retinopathy	Hypertension	Hyperlipidemia	Reference
Vaccinium myrtillus	Ericaceae				☑			[191]
Vitis vinifera	Vitaceae	☑	☑	☑	☑			[182, 187, 192]
Withania somnifera	Solanaceae							[193, 194]
Zingiber officinal	Zingiberaceae			☑				[165, 195]

Table 2 Mechanism actions of medicinal plants on diabetes and its complications

Scientific name	Family	Mechanism	Reference
Anacardium occidentale Linn.	Anacardiaceae	The antihyperglycemic and nephroprotective effects are related to reducing diabetes-induced functional and histological alterations in the kidneys and reduced accumulation of mucopolysaccharides in the kidneys.	[165]
Annona squamosa Linn.	Annonaceae	The antidiabetic and hypoglycemic effects of this plant are associated with increased insulin levels in the pancreatic islets, increased glucose consumption in the muscles, and inhibition of hepatic glucose uptake.	[76]
Annona muricata Linn.	Annonaceae	Reduction of oxidative stress on pancreatic B cells. The treatment increased the area of insulin immunoreactive B cells and partially prevented degeneration of B cells	[78]
Boerhaavia diffusa Linn.	Nyctaginaceae	The antidiabetic effects of this plant are caused by lowering blood glucose levels and increasing insulin sensitivity.	[89]
Bougainvillea spectabilis Linn.	Nyctaginaceae	The antihyperglycemic effects induced by this plant are due to the increased conversion of glucose to glycogen in the kidney and increased insulin sensitivity.	[92]
Bridelia ndellensis Beille.	Euphorbiaceae	Antidiabetic effects of this plant cells and requires functional B-cell islets	[196]
Canavalia ensiformis DC.	Leguminosae	The antihyperglycemic and antihyperlipidemic effects of this plant are due to its decreasing blood glucose and urine levels, as well as its decreasing triglyceride, ketone bodies, and cholesterol associated with diabetes mellitus.	[197]
Casearia esculenta Roxb.	Flacourtiaceae	The hypoglycemic effects induced by this plant are associated with reduced blood glucose levels and affecting the metabolism of proteins and marker enzymes.	[103]
Cassia kleinii Wight & Arn.	Caesalpiniaceae	Reducing blood glucose levels	[104]
Catharanthus roseus Linn.	Apocyaceae	The mechanism of hypoglycemic action of this plant is associated with prophylactic activity against necrotic actions.	[198]
		Affecting carbohydrate metabolism enzymes.	
		Increasing insulin secretion.	
		Helping prevent damage due to free radical oxygen and exerting antioxidant effects.	
		Increasing glucose uptake in tissues	
Coccinia indica Wight & Arn.	Cucurbitaceae	Exerting B ell restorative properties against alloxan induced damage	[199]
Cocculus hirsutus Linn.	Menispermaceae	Exerting antihyperglycemic effects by reducing serum glucose levels and increasing glucose resistance.	[123]
Coscinium fenestratum Colebr.	Menispermaceae	Regulating the metabolism and improving the antioxidant effects. Regulating the glucose homeostasis and reducing gluconeogenesis. Exerting supportive effect on the antioxidant defense of the cell.	[124]
Dioscorea dumetorum Pax.	Dioscoreaceae	Exerting antihyperlipidemic effects in the body by controlling hyperketonemia and hypercholesterolemia.	[139]
Ficus hispida Linn.	Moraceae	Reducing fasting blood glucose levels by directly influencing beta cells	[141]
Hypoxis hemerocallidea Fisch. Mey.	Hypoxidaceae	The mechanism of the hypoglycemic effect of this plant has not yet been determined yet.	[153]
Murraya koenigii Linn.	Rutaceae	Exerting hypoglycemic effects by increasing liver glycogen concentration and affecting carbohydrates metabolism	[200]
Panax ginseng Linn.	Araliaceae	Exerting hypoglycemic effects by affecting the metabolism of carbohydrates.	[165]
Syzyguim cumini Linn.	Myrtaceae	Hypoglycemic effects can be exerted via different mechanisms only in disease conditions and in diabetic people.	[185]
Terminalia chebula Retz	Combretaceae	This plant has renoprotective action.	[186]
Terminalia catappa Linn.	Combretaceae	Exerting antidiabetic and antihyperglycemic effects through regeneration of beta cells due to B-carotene in reducing diabetic complications like glycosylation	[187]

Increased, Up-regulation, and Translocation of Glucose Transporter Type 4

Glut-4 is one of the most important insulin-regulated glucose transporters located at the surface membrane of adipocytes, skeletal and cardiac muscle cells. A triterpenoid constituent of *M. charantia* fruit, cucurbitane [45], stimulates GLUT-4 cell membrane translocation to facilitate glucose uptake and AMP-activated protein kinase (AMPK) phosphorylation [46–48]. A comparable effect occurs with an extract of *A. cepa* [49]. Likewise, in mouse adipocytes, an aqueous extract of Cinnamon evokes a biphasic action on GLUT-4 mRNA [50] whereas an active constituent of the plant, cinnamaldehyde, increases glucose uptake through augmented GLUT-4 translocation [51]. Ginsenoside-Rh2 present in *P. ginseng* decreases plasma glucose in diabetic rats by increasing GLUT-4 expression via a more indirect mechanism arising from elevated β-endorphin stimulation of μ-opioid receptors [52].

Insulin Resistance Reduction

Insulin resistance (IR) is a pathological condition in which cells do not respond normally to insulin. In this respect, *Ocimum sanctum* (Holy basil) delays the onset of IR in rats and has been proposed as an adjuvant therapy for patients who develop this condition [53]. Also, in rats, meliacinolin isolated from the leaves of *A. indica* inhibits IR among a number of other antidiabetic modes of action [31]. Analogously, *M. charantia* ameliorates IR in mice though the underlying mechanism has been hypothesized to be through PPAR-γ-mediated pathways [54].

There are over 400 plant species with hypoglycemic properties. However, the study of new antidiabetic, plant-derived drugs is still pursued and continues to draw attention because of potential safety issues. Most of the plants contain alkaloids, glycosides, terpenoids, flavonoids, and carotenoids, to which their antidiabetic properties have been attributed. Several medicinal plants such as *Galega officinalis*, in addition to producing positive effects on glucose homeostasis in patients with DM, have found application in preventing and treating hypertension, cardiovascular disease, and kidney injury [13, 55, 56•, 57]. In addition to producing hypoglycemic effects, numerous plants have been demonstrated to be effective against the wide range of diabetic complications (Table 1). In Table 2, the mechanisms of the effects of these plants are summarized.

Conclusion

Problems arising from IR and chronic hyperglycemia have become a major concern in clinical science and drug therapy. Medicinal plants have usually attracted attention conceivably due to fewer side effects than chemically synthetic drugs. The antihyperglycemic effects of the plants presented in this article are essentially related to their ability to maintain pancreatic function and insulin output facilitating anabolic activities such as muscle, adipocyte, and hepatic glucose uptake as well as glucose-to-glycogen conversion.

Oxidative stress induced by hyperglycemia plays an important role in the expansion of the extracellular matrix and glucose-induced collagen production [201]. When endothelial cells respond to increased glucose, the production of reactive nitrogen species and ROS increases. The production of these reactive substances triggers single-strand breakage of DNA, and subsequently increases the levels of 8-hydroxyguanine and 8-hydroxydeoxy guanosine (markers of oxidative stress-induced DNA damage) in plasma and tissues. The concentrations of these products can be restrained by controlling hyperglycemia and using antioxidants [202]. Studies have shown that the use of antioxidants has been successful in preventing DM-induced disorders, including neuropathy, nephropathy, and retinopathy. High doses of single antioxidants, such as vitamin E or C, may interfere with the antioxidant-provident balance in the cellular system, so it has been suggested that a mixture of therapeutic antioxidants with trace elements and vitamins may be used to improve the metabolic system [203]. More importantly, single antioxidants may not be able to counteract all free radical species; hence, medicinal plants which possess a wide range of phytochemicals with antioxidant activities may be more efficient.

Although treatment with medicinal plants has significant effects on pancreatic β cell-reducing blood glucose levels as well as other DM-related complications, there is scant information on their biology, especially on how they actually affect DM. However, it has been shown that most medicinal plants contain compounds such as glycosides, alkaloids, terpenoids, and flavonoids, which mitigate DM by exerting antioxidant effects and other related activities [68–70]. Taken together, although plants may have antidiabetic effects with their own specific action mechanism, almost all of them display antioxidant properties and a range of other contributory actions. Given that oxidative stress is one of the main causes of DM and its related disorders, it is likely that the antioxidant effect of these plants plays a major role in their effectiveness.

Finally, it can be concluded that medicinal plants that produce a profile of concomitant effects may be considered alternative or adjunctive drugs for the treatment or prevention of DM and its complications. It is, however, essential to study the effects of medicinal plants on DM in more detail in order to obtain further data on the biology and pharmacological effects of these plants.

Compliance with Ethical Standards

Conflict of Interest Zeinab Nazarian-Samani, Robert D. E. Sewell, Zahra Lorigooini, and Mahmoud Mahmoud Rafieian-Kopaei declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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